

EDITORIAL COMMENT

Renin-Angiotensin System Blockade and Improved Clinical Outcomes in Chronic Aortic Regurgitation

Enough Ammunition to Revise Guidelines, or Do We Need a Randomized Controlled Trial?*

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The natural history of chronic aortic regurgitation (AR) is characterized by a series of left ventricular (LV) compensatory mechanisms. Initially, the regurgitant volume is accommodated by increases in LV end-diastolic volume and compliance and associated LV hypertrophy. However, the concomitant increased wall stress results in increased afterload and, with it, more hypertrophy. Thus, chronic AR imposes both a volume and an often underappreciated pressure load on the left ventricle (1). The natural history of the condition typically includes a long plateau phase during which LV ejection performance is maintained and patients remain asymptomatic, and it is theoretically appealing that medical intervention at this point might improve outcomes, notably the need for aortic valve replacement (AVR) and the development of heart failure.

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Candidate pharmacologic agents have included calcium-channel blockers, notably nifedipine, as well as beta-blockers and drugs that target the renin-angiotensin system. Much of what we know about the impact of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in the setting of severe AR is derived from rat studies reported by the group at Laval, Quebec, Canada. In 2003, Plante et al. (2) reported that ACE activity and fibronectin expression were increased in

rats with chronic severe AR and that both could be reduced by high-dose but not low-dose captopril therapy. Subsequently, using the same model of chronic severe AR, this group reported the up-regulation of genes encoding for procollagen types I and III, fibronectin, atrial natriuretic peptide, transforming growth factor- β (2), and connective tissue growth factor. Treatment with metoprolol and captopril variably reduced this up-regulation (3). In 2009, Plante et al. (4) compared the impact of 3 vasodilators—nifedipine, captopril, and losartan—in male rats with AR. Although nifedipine-treated animals were similar to controls with regard to hemodynamic parameters, LV dilation, hypertrophy, and loss of systolic function, captopril or losartan slowed the onset of these abnormalities (4). However, when, in a similar model, AR was accompanied by systemic hypertension, captopril was much less effective (5).

Despite these promising studies, there are limited and conflicting data concerning the results of renin-angiotensin system blockade in humans. Lin et al. (6) reported that a dose of 20 mg twice daily of enalapril favorably influenced LV remodeling at 1 year in patients with mild to severe AR, while Banaszewski et al. (7) reported favorable acute and long-term (12 to 53 months) effects of captopril in patients with moderate and severe AR, although the study included no control group. However, the prospective randomized controlled trial of Evangelista et al. (8) in patients with chronic severe AR showed no effect of either enalapril (20 mg/day) or nifedipine in time to AVR or echocardiographically assessed AR volume and LV function. Similarly, a small retrospective analysis of 18 pediatric patients failed to show a benefit of ACE inhibitor therapy (9).

In this issue of the *Journal*, Elder et al. (10) report the results of a retrospective longitudinal cohort study of patients with echocardiographic diagnoses of moderate or severe AR, comparing those who did versus those who did not receive ACE inhibitors or ARBs.

Their study takes advantage of their ability to use the echocardiographic records from a single hospital to identify patients with moderate or severe AR and to combine this information with regional medical databases that include pharmacy as well as morbidity and mortality (cardiovascular and all-cause) outcomes. The goal was to test the hypothesis that ACE inhibitor or ARB use improves outcomes in patients with moderate to severe AR.

There is limited information in this report concerning concomitant cardiac and noncardiac disease, and there are no apparent exclusions for those with mixed valvular disease. Although there were high death and overall event rates, only 62 patients underwent AVR, precluding a meaningful analysis limited to this outcome. Similarly, the investigators are unable to provide information concerning worsening severity of AR. Thus, the analysis focuses on differences in all-cause mortality, cardiovascular, and AR events (heart failure hospitalizations, heart failure deaths, or AVR) between patients treated with and without ACE inhibitors or ARBs.

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The investigators are to be commended for taking advantage of their databases to provide an analysis of more than 2,000 patients, by far the largest clinical study evaluating medical outcomes in patients with AR. Additionally, acknowledging the differences between groups exposed or not exposed to ACE inhibitors or ARBs with regard to a number of important baseline demographic, echocardiographic, and clinical characteristics, they used propensity matching and time dependency analysis to try to tease out whether the observed differences represent a cause-effect relationship or spurious findings. They also performed subgroup analysis between those with and without LV systolic dysfunction and those with and without LV dilation.

The major finding was reduced all-cause mortality and cardiovascular and AR events in the group treated with ACE inhibitors or ARBs. However, is this strong enough ammunition for revising guidelines or generating support for a randomized controlled clinical trial?

Potential Biases and Unappreciated Confounding

Mixed valve disease and echocardiographic grading. All retrospective cohort studies are limited by methodologic issues and potential sources of bias that even sophisticated statistical analyses cannot completely overcome. In this study, one concern relates to the apparent failure to define the study cohort as patients with pure AR. Because aortic valve disease is frequently a mixed process, it is possible that the benefit of ACE inhibitors or ARBs was predominantly in those with concomitant aortic stenosis (AS). To this point, the same group has just published data from a similar analysis of the databases used for this study, with a focus instead on AS. They reported an association between ACE inhibitor or ARB therapy and more favorable outcomes in patients with AS (11). This begs the question of whether the apparent impact of ACE inhibitor or ARB therapy in this study of AR could in fact be due to its effect on AS, or, conversely, was the “beneficial” effect in patients with AS actually attributable to concomitant AR? The presence of unrecognized mitral disease is a related and unaddressed potential confounding variable. If, as might be anticipated, this group goes on to assess treatment-associated outcomes in groups with other forms of valvular disease, it is hoped that the study groups will be limited to those with a single type of valve dysfunction.

In this study, another concern is the validity of the echocardiographic grading of AR and the possibility of information bias in the diagnosis of patients with moderate or severe regurgitation. The echocardiographic community has recognized the challenges of accurate and reproducible assessment of the severity of valve regurgitation and has published guidelines that include the use of quantitative measures (vena contracta, effective regurgitant orifice, regurgitant volume, and regurgitant fraction) (12) in addition to the measures of jet dimensions, descending aortic flow, and pressure half-time that were used in this study. Regur-

gitant volume and effective regurgitant orifice area have been reported to supersede traditional AR grading in predicting overall survival and survival free of AVR under medical management as well as cardiac events, including cardiac death, congestive heart failure, and new episodes of atrial fibrillation (13). Thus, the message of this study would have been stronger had a more integrated approach to AR grading been used and had the investigators presented intraobserver and interobserver variability analyses on a subset of patients from the echocardiographic database, including those with mild AR. This would help allay the concern that, in the context of the overall study findings, there might have been a tendency to upgrade the severity of regurgitation in the cohort of patients receiving ACE inhibitor or ARB therapy, particularly those with larger left ventricles and/or those receiving diuretic agents. Perhaps the cohort of patients not receiving ACE inhibitors or ARBs actually included patients with more severe regurgitation than was appreciated.

What about the adrenergic system? As previously noted, the Laval group has reported that both beta-blockers and ACE inhibitors had favorable effects on gene up-regulation in a rat model of AR (3). Additionally, in 2004, Plante et al. (14) reported that metoprolol favorably influenced LV remodeling and systolic dysfunction in rats with chronic severe AR and that, at 1 year, metoprolol improved survival, minimized LV hypertrophy, improved LV filling pressures, decreased LV subendocardial fibrosis, and helped restore the beta-adrenergic receptors (15). This leads one to consider the potential for the results of this study to be confounded by concomitant beta-blockade. Indeed, even in the propensity-matched analysis, the group receiving ACE inhibitor or ARB therapy included patients with significantly greater use of beta-blockers, begging the question of whether beta-blockers and not ACE inhibitors or ARBs were the true source of the apparent benefit. Interestingly, calcium-channel blockers, aspirin, nitrates, statins, diuretic agents, and digoxin were also used more frequently in the ACE inhibitor or ARB group, even in the propensity-matched analysis. Although the investigators argue that these may be markers of symptomatic heart failure in the ACE inhibitor or ARB group (i.e., making them “sicker” and at greater risk), it is equally possible that any or all of these agents may have been the basis for the improved outcomes in the ACE inhibitor or ARB group.

Nonvalvular heart disease. It is difficult to ignore the impulse to play detective in identifying other forms of heart disease that were differentially present in the groups with versus without ACE inhibitor or ARB therapy, and one that immediately comes to mind is coronary disease, the presence of which would explain the increased prevalence of aspirin, beta-blockers, nitrates, and calcium-channel blockers. Is it possible that the primary benefit of ACE inhibitors or ARBs was in those with coronary disease? Speculation along these lines could be endless.

A final general category of bias relates to the outcomes selected for analysis. In this study, relatively few patients ($n = 62$) underwent AVR, and thus, the major emphasis of the report is on improved heart failure–related outcomes. Although heart failure is a recognized outcome of chronic severe AR, it is, at best, a nonspecific one, and the small number of AVRs given the overall prevalence of moderate and severe AR leads one to ask for more information concerning both surgical referral practices in the medical community studied as well as the link between AR and heart failure as perceived clinically. In other words, it is hard to reconcile the small number of AVRs with the relatively large number of heart failure–related events, because AVR carries a Class I indication for patients with severe AR with symptoms and/or LV systolic dysfunction (16).

Enough ammunition to revise guidelines, or do we need a randomized controlled trial? The current American College of Cardiology and American Heart Association guidelines for the treatment of patients with AR suggest that vasodilators be reserved for patients who are symptomatic and/or have LV dysfunction and who are not candidates for AVR (Class I) and as a short-term therapy in patients who will undergo AVR (Class IIA), leaving as a Class IIB indication their use in asymptomatic patients with normal LV systolic function but LV dilation (16). The results of this study are insufficient to justify an alteration of these recommendations.

However, perhaps they do justify support for a multicenter randomized controlled trial with a sample size and study design robust enough to provide a definitive answer to the question of whether pharmacologic therapy can influence the natural history of severe AR. In the most recent American College of Cardiology and American Heart Association guidelines for the management of patients with valvular heart disease, there is only one indication supported by Level of Evidence: A (data derived from multiple randomized clinical trials) and a disturbingly large number supported only by the consensus opinion of experts, case studies, or standard-of-care (Level of Evidence: C) (16). Given the prevalence and clinical importance of valvular heart disease, surely we can commit to studies that will provide a robust evidence base for therapy.

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